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Case Report

Post-COVID-19 fibromyalgia syndrome: A report of two cases

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Abstract
COVID-19 is a viral infection caused by SARS-CoV-2 that primarily targets the respiratory system. COVID-19 may be followed in some patients by post-COVID-19 syndrome, fatigue, anxiety, and musculoskeletal pain. These symptoms may be associated with other symptoms, resulting in a constellation of symptoms consistent with fibromyalgia syndrome (FMS). Two patients were evaluated at the rheumatology outpatient clinic for diffuse persistent musculoskeletal pain after COVID-19 infection. Patients presented with generalized musculoskeletal pain, fatigue, anxiety, depression, headache, hand paresthesia, and non-restorative sleep. General examination and various laboratory investigations, including autoimmune profile and radiological investigation, were normal. After examining eighteen tender points, both patients fulfilled the 1990 ACR classification criteria for FMS. Post-COVID-19 FMS should be considered during the management of post-COVID-19 syndrome to alleviate pain and prevent worsening of symptoms during the COVID-19 pandemic.

Keywords
COVID-19, Fibromyalgia Syndrome, Fatigue

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Introduction

In December 2019, an outbreak of a novel coronavirus infection by SARS-COV-2 in China had become an international health emergency, causing coronavirus disease-19
(COVID-19) [1]. The Coronaviridae family is a single-stranded RNA genome. Viral RNA released in host cell cytoplasm starts processes of translation, transcription, and replication, leading to downregulation of the Angiotensin-converting enzyme 2 (ACE2) receptors. As the immune system responds by expression of ACE2 of the host cell surface that binds to spike glycoprotein of the viral envelope, which in turn results in the release of angiotensin 2 and will stimulate type1a angiotensin 2 receptors in the lung, increasing pulmonary vascular permeability and lung damage [2]. The diagnosis for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection is largely based on Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) with a high rate of false-negative results and has been found largely inferior to that of a chest computed tomography. The most common manifestations associated with SARS-CoV-2 infection are fever, headache, chest pain, nausea, musculoskeletal pain, anxiety, fatigue, impaired visual acuity, depression, confusion, post-traumatic stress symptoms, and cognitive impairment [1]. Since the recognition of SARS-CoV-2 infection in late 2019, there were clinical and laboratory emphasis on the respiratory manifestations. Post-covid syndrome is not merely one condition; it is defined by the National Institute for Health and Care Excellence (NICE) as "signs and symptoms that develop during or after COVID-19 infection and continue for more than 12 weeks that not explained by another diagnosis [3]. Fatigue was one of the most common longer-term consequences of viral infection, Post-infectious fatigue and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) has also been observed after the onset of other epidemics like the Spanish Flu and the outbreak of the SARS-CoV virus, causing an epidemic of SARS in 2003, it is also observed in people recovering from H1N1 [4]. Acute or chronic stress may trigger or aggravate the symptoms of Fibromyalgia Syndrome (FMS) [5] Fibromyalgia syndrome (FMS) is a chronic diffuse widespread pain condition associated with other symptoms, including morning stiffness, anxiety, fatigue, sleep disturbance, cognitive problems, and 18 tender points [6]. It may result from or coexist with neuro-hormonal or immunologic disorders, genetic predisposition, infections, rheumatic diseases, physical trauma, or psychological illness [6].

Case Report

Case 1

The patient was a 43-years-old housewife who started to develop fever, generalized muscle and bone pain, dry cough, and severe shortness of breath. She was known to have controlled type 2 diabetes. Her investigations revealed: Hb 13.0 g/dl, WBC of $9.0x10^3/mm^3$ with relative lymphopenia, platelets of $226x10^3/mm^3$. The ESR was 58 mm/1st h, the CRP was positive (20.3 mg/L), D-dimer 360 ng/mL, ALT 16 U/l, AST 20 U/l, and HbA1c: 9.2%. PCRs for COVID-19, was positive. CT chest was normal. She was diagnosed with a case of COVID-19 infection and was given azithromycin 500 mg/day, aspirin at a low dose of 100 mg/d for 3 months, zinc, vitamin C, and vitamin D supplement. There was an improvement in her chest symptoms, normalized body temperature. However, the patient still complained of generalized muscle and bone pain, fatigue, and stiffness, especially in the early morning. Three months later, she developed progressive sleep disturbance, mood disturbance, anxiety with depressive symptoms. The patient was advised to take painkillers and to have a stress-free lifestyle, but with no improvement, investigations revealed Hb 13.7 g/dl, WBC $9.5x10^3/mm^3$, platelets of $282x10^3/mm^3$. CRP: 4.4 mg/L, serum ferritin: 80.1 ng/mL, D-dimer 250 ng/mL, ANA, RF and anti-CCP were negative. After a rheumatologic consultation, the diagnosis of FMS secondary to COVID 19 was considered with 15/18 tender points [6]. Amitriptyline tablet 25 mg/day with vitamin D, vitamin C, and zinc supplement was started, and a month later, there was modest improvement in her wellbeing and mood status with12/18 tender points.

Case 2

A 42-year-old worker presented with severe bone pain, myalgia, dyspnea, fever, and dry cough. He was a chronic heavy cigarette smoker 20 cigarettes/day and was apparently healthy and had no chronic diseases. His investigations revealed normocytic normochromic anemia, leukocytosis $12.3x10^3/mm^3$, ESR 50, and CRP 12.8 mg/L. A chest x-ray revealed exaggerated bronchovascular markings. A chest CT showed pneumonic patches for which he received multiple antibiotics but with mild improvement. A nasopharyngeal swab was analyzed by RT-PCR and confirmed a SARS-CoV- 2 infection. His D-dimer was 320 ng/mL. He received azithromycin 500 mg/day orally for 5 d, hydroxychloroquine 400 mg/day, zinc, vitamin C and vitamin D supplements, mast cell stabilizer with moderate improvement. As the chest pain persisted, he quit smoking. Three months later, he developed sleep disturbance, severe generalized muscle and bone pains, morning stiffness, anxiety, and fatigue that lasted for further 3 months. The patient consulted a psychiatrist and was prescribed Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) for three weeks with mild improvement. After a rheumatological consultation, he was diagnosed with FMS according to the 1990 ACR criteria [6] with 17/18 tender points. Duloxetine 60 mg/day at night was added to his treatment. The patient was advised to lead a stress-free lifestyle, vitamin D, vitamin C, and zinc supplements were provided. At the follow-up examination three months later, the general condition of the patient improved. On examination, there were fewer tender points 11/18. The patient continued on the same medications with reassurance.

Discussion

There are some different common underlying etiopathogenesis between COVID-19 and FMS. Researchers found that patients who contracted COVID-19 exhibited a 'cytokine storm.' Specifically, patients had increased levels of IL-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein-α, and tumor necrosis factor- α. Also researchers found associations between single nucleotide polymorphisms in cytokine genes and post-infection complications such as fatigue, pain, neurocognitive difficulties, and mood disturbances. Specifically, the associations were

found with IL-6, TNF-α, IFN-γ, and IL-10. Furthermore, the researchers found that increased fatigue post-infection was associated with T allele of IFN-γ +874 T/A SNP [7]. The cytokine storm experienced during the illness may persist and contributes to other complications such as prolonged fatigue. Cytokines that have been implicated in both post-infectious ME/CFS and COVID-19 such as IL-2, granulocyte-colony stimulating factor, and interferon-γ inducible protein 10 [7]. From another perspective, inhibition of ACE 1 can enhance pain by blocking the degradation of substance P and bradykinin and enhancing kinin receptors signaling, resulting in fibromyalgia-like symptoms. Furthermore, the association of Angiotensin-Converting Enzyme 1 (ACE-1) gene polymorphism with FMS development has been addressed in the literature [2]. The spike protein on the virus binds the ACE2 receptor, facilitating the entry into human cells and provoking antagonistic pathways of the renin-angiotensin system results in an imbalance of the ACE/ Angiotensin II and its receptor as well as the ACE2/ angiotensin /Mas receptor pathways. By inducing a decrease in membrane ACE2 receptors on host cells, an imbalance of ACE/ACE2 occurs that contributes to the pathogenesis of SARS-CoV-2 infection and triggers severe lung injury [2]. In addition, the stress associated with the lock-down due to the COVID-19 pandemic leads to increased musculoskeletal pain, and numerous patients developed different FMS symptoms [5]. Since hypertension is a frequent late effect of COVID-19 and is comorbidity affecting FMS patients, in such cases, hypertension treatment with ACE inhibitors should be avoided, and other classes of antihypertensive drugs should be preferable [8]. Evidence suggests that these medications can upregulate the expression of angiotensin-converting enzyme 2 (ACE2), the cellular receptor for SARS-CoV-2. Thus, it is hypothesized that ACE2-increasing drugs could increase the risk of infection and prompt a more severe clinical course in hypertensive patients, which in turn may be related to post-COVID-19 sequelae like FMS [8].

Conclusion

FMS can be significant comorbidity in previous COVID infection. Post-COVID-19 FMS should be considered during the management of post-COVID-19 syndrome to alleviate pain and prevent worsening of symptoms during the COVID-19 pandemic.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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